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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

**In Re Application of:**

Phillip Dan Cook

**Serial No.:** 08/884,873

**Group Art Unit:** 1627

**Filing Date:** June 30, 1997

**Examiner:** M. Garcia

**For:** NUCLEOBASE HETEROCYCLIC COMBINATORIALIZATION

**DATE OF DEPOSIT:** 19 NOVEMBER 2001

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TO THE ASSISTANT COMMISSIONER FOR PATENTS,  
WASHINGTON, DC 20231.

TYPED NAME: Paul K. Legaard  
REGISTRATION NO.: 38,534

Assistant Commissioner for Patents  
Washington DC 20231

**TRANSMITTAL OF APPEAL BRIEF**

1. Transmitted herewith in triplicate is the APPEAL BRIEF in this application  
with respect to the Notice of Appeal filed on September 21, 2001.

2. **STATUS OF APPLICANT**

- ☒ Applicant(s) has previously claimed small entity status under 37 C.F.R.  
§1.27.
- ☐ Applicant(s) by its/their undersigned attorney, claims small entity  
status under 37 C.F.R. §1.27 as:
- ☐ an Independent Inventor
- ☐ a Small Business Concern

☐ a Nonprofit Organization.

### 3. EXTENSION OF TERM

The proceedings herein are for a patent application and the provisions of 37 CFR 1.136 apply.

☐ Applicant petitions for an extension of time under 37 CFR 1.136 (fees: 37 CFR 1.17(a)-(d)) for the total number of months checked below:

	SMALL ENTITY		NOT SMALL ENTITY	
<input type="checkbox"/> ONE MONTH EXTENSION OF TIME	\$55	\$	\$110	\$
<input type="checkbox"/> TWO MONTH EXTENSION OF TIME	\$200	\$	\$400	\$
<input type="checkbox"/> THREE MONTH EXTENSION OF TIME	\$460	\$	\$920	\$
<input type="checkbox"/> FOUR MONTH EXTENSION OF TIME	\$720	\$	\$1440	\$
<input type="checkbox"/> FIVE MONTH EXTENSION OF TIME	\$980	\$	\$1960	\$
<input type="checkbox"/> LESS ANY EXTENSION FEE ALREADY PAID	minus	(\$ )	minus	(\$ )
<input checked="" type="checkbox"/> APPEAL BRIEF	\$160	\$160.00	\$320	\$
TOTAL FEE DUE		\$160.00		

### 4. FEE PAYMENT

- ☒ A check in the amount of \$ 160.00 is attached. Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050.
- ☐ Please charge my Deposit Account No. 23-3050 in the amount of \$\_\_\_\_. A duplicate of this transmittal is attached.

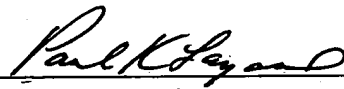
### 5. FEE DEFICIENCY

- ☒ If any additional extension and/or fee is required, this is a request therefor and to charge Deposit Account No. 23-3050.

☒ If any additional fee for claims is required, charge Deposit Account No. 23-3050.

6. ☒ The Commissioner is hereby requested to grant an extension of time for the appropriate length of time, should one be necessary, in connection with this filing or any future filing submitted to the U.S. Patent and Trademark Office in the above-identified application during the pendency of this application. The Commissioner is further authorized to charge any fees related to any such extension of time to deposit account 23-3050. This sheet is provided in duplicate.

Date: 19 NOVEMBER 2001

  
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Phillip Dan Cook

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For: NUCLEOBASE HETEROCYCLIC COMBINATORIALIZATION

I, Paul K. Legaard, Registration No. 38,534 certify that this correspondence is being deposited with the U.S. Postal Service as First Class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

On November 19, 2001

  
Paul K. Legaard Reg. No. 38,534

BOX AF

Assistant Commissioner for Patents  
Washington, D.C. 20231

Dear Sir:

**APPELLANT'S BRIEF PURSUANT TO 37 C.F.R. 1.192**

Appellant appeals the Final Rejection mailed May 21, 2001 in connection with the above-identified application. An Amendment under 37 C.F.R. 1.116 was filed July 19, 2001, but was not entered. An Advisory Action mailed August 3, 2001 reaffirmed the rejections set forth in the Final Rejection. A Notice of Appeal with appropriate fees was filed September 21, 2001.

**I. Real Party in Interest**

The real party in interest in the above-identified patent application is ISIS Pharmaceuticals, Inc., a corporation of Delaware, which is the assignee of Phillip Dan Cook.

## II. Related Appeals and Interferences

There are no other appeals or interferences known to Appellant, Appellant's legal representative, or the assignee that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending Appeal.

## III. Status of Claims

The present application was filed with original claims 1-36. Claims 1, 6, 13-32 and 34-36 were cancelled during prosecution. Claims 2-5, 7-12 and 33 are on appeal; they appear in Appendix A.

## IV. Status of Amendments

Following the Final Rejection, Appellant amended claim 35 in the Amendment under 37 C.F.R. 1.116 filed July 19, 2001. The Advisory Action mailed August 3, 2001, indicated that the Amendment would not be entered<sup>1</sup>.

## V. Summary of the Invention

Appellant's claimed invention is directed to a mixture of at least six chemical compounds that have a common heterocyclic scaffold. The heterocyclic scaffold bears functionalizable atoms. Chemical species are bonded to a functionalizable atom of the heterocyclic scaffold through the intermediation of a tether moiety. The chemical compounds in the mixture can be prepared in an iterative manner. For example, all but one functionalizable atom on the heterocyclic scaffold can be blocked and the remaining functionalizable atom reacted with a tether to give rise to a tethered heterocyclic scaffold. The tethered heterocyclic scaffold can be further reacted with chemical

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<sup>1</sup> A copy of the Amendment filed in response to the Final Rejection is attached hereto as Exhibit B. The Final Rejection rejected claims 2-5, 7-12 and 33 as allegedly being obvious in view of the combination of three references. Appellant amended the sole independent claim (*i.e.*, claim 33) to delete the feature that was alleged to be obvious. Because the amendment to claim 33 removed an issue for appeal (*i.e.*, obviousness), Appellant requested that it be entered into the record, citing M.P.E.P. § 714.12. The Advisory Action indicated that the proposed amendment would not be entered because it allegedly raised new issues that would require further consideration and/or search. Although Appellant maintains that the amendment should have been entered, upon return of the application to the Examiner, Appellant plans to file an RCE to gain entry of the proposed amendment if such proposed amendment is not entered upon return of the application to the Examiner.

substituents. By iterative cycles of blocking and deblocking, a mixture of increasingly complex compounds can be prepared.

## VI. Issues

The only issues that Appellant proposes to contest in this appeal are: 1) whether claims 2-5, 7-12 and 33 are unpatentable under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter<sup>2</sup>; and 2) whether claims 2-5, 7-12 and 33 are unpatentable under 35 U.S.C. § 102(a) as allegedly being anticipated by WO 96/33972 (hereinafter, the "Gordeev reference").

## VII. Grouping of the Claims

For the purposes of this Appeal, Applicants submit that claims 2-5, 7-12 and 33 stand or fall together.

## VIII. Arguments

### A. Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 2-5, 7-12 and 33 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing "new matter." Claim 33 recites a mixture comprising a set of at least six chemical compounds having a common heterocyclic scaffold bearing functionalizable atoms. The set of compounds is represented by one of three heterocyclic scaffold structures -- I, II, or III. Each of the heterocyclic scaffold structures bears three "T" moieties to each of which is bound a chemical substituent "L." Claim 33 further recites a list of "T" moieties in the alternative form. Prior to Appellant's Amendment, the relevant portion of claim 33 recited the following:

each tether moiety T is a single bond or -NH(R<sup>1</sup>)NH-, -NH(R<sup>1</sup>)O-, -NHR<sup>2</sup>NH-, -NHR<sup>2</sup>SO<sub>2</sub>NH-, -NHR<sup>1</sup>-, -N(R<sup>4</sup>)<sub>2</sub>-, -N=N-, O, S, Se, -P(=O)(O)<sub>2</sub>, NH, OR<sup>2</sup>, OR<sup>3</sup>, malonato, pyrrolidinyl, piperidinyl, piperazinyl, or morpholino;

In response to an anticipation rejection, Appellant amended claim 33 to delete "a single bond or." The Final Rejection erroneously concludes that deletion of "a single bond or" as an option for the

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<sup>2</sup> The new matter rejection is an appealable rejection because it touches the claims. See, M.P.E.P. § 608.04(c).

“T” moiety created a “sub-genus” for which Appellant’s specification lacks support. Thus, the erroneous position taken in the Final Rejection is that Appellant’s specification only supports mixtures of compounds wherein at least one compound must have a single bond for the “T” moiety. This rejection is improper and should be reversed for the following reasons.

The specification provides ample written description of mixtures of compounds that fall within the scope of claim 33 wherein each “T” moiety is one of the tethers recited in the claim (*i.e.*, where T is other than a single bond). Indeed, Appellant’s specification provides general, broad teachings as well as numerous working examples whereby mixtures of compounds having a “T” moiety that is a tether, as opposed to a single bond. For example, page 2, lines 28-31 of the specification teaches:

The chemical species may either be bonded directly [*i.e.*, where T is a single bond] to a functionalizable atom on the heterocyclic scaffold or may be so bonded through the intermediation of a tether moiety [*i.e.*, where T is other than a single bond].

In addition, page 3, lines 27-32 of the specification teaches:

The tether moieties which may be employed in connection with the present invention are optional. That is, they may, but need not, be caused to be inserted between the chemical substituents and the heterocyclic scaffold molecules in order to provide further diversity in the resulting mixtures of compounds.

Appellant’s specification clearly teaches one skilled in the art that the tether moieties (*i.e.*, the “T” moieties) can either be present between the chemical substituents and the heterocyclic scaffold or can be absent. Thus, the specification clearly allows a person skilled in the art to clearly recognize that Appellant had possession of the claimed invention where “T” is other than a single bond.

Indeed, even the Final Rejection acknowledges at page 3, referring to libraries 59-62 and Examples 109-113 of Appellant’s specification, that “these examples show selections for T that are not single bonds.” The Final Rejection quite confusingly adds, however, that “it is not clear support for the removal from the claim of such a limitation.” The Final Rejection further states that:

There are several examples in the specification that *do* depict T as a single bond and applicant does not appear to be in possession of the “sub-generic” libraries that specifically limit T to other than a bond.

Whether or not Applicant's specification provides several examples where T is a single bond certainly does not detract in any way from the numerous examples where T is other than a single bond. Indeed, the Final Rejection has already acknowledged that Appellant's specification provides examples that "show selections for T that are not single bonds." Thus, the reasoning set forth in the Final Rejection is internally contradictory.

The Final Rejection further appears to take the erroneous position, even in view of the broad language and numerous working examples in the specification, that the specification requires that all the tethers recited in claim 33 be grouped into a single aggregation or collection and that elimination of one particular species of tether creates a "sub-genus" for which the specification allegedly lacks support. Quite telling, however, the Final Rejection fails to point to any portion of Appellant's specification to support such a conclusion. In fact, there is no disclosure in the present specification that every mixture of chemical compounds is required to have a compound wherein the "T" moiety is a single bond. Indeed, the very language of claim 33 supports the opposite conclusion. Claim 33 does not recite that "T" is a mixture of moieties comprising the recited species. Rather, the options for the "T" moiety are presented in the alternative form (*i.e.*, using commas followed by "or"). Further, the specification teaches, for example, at page 10, lines 9-21:

It will be appreciated that one of the more significant aspects of the present invention is the ability to proceed iteratively. In this regard, all but one functionalizable atom on the heterocycle, *e.g.* the preferred purine, pyrimidine or piperazine, is chemically blocked and the remaining functionalizable atom reacted with a set of chemical substituents (or with a tether) to give rise to a mixture of chemical compounds or a tethered scaffold. Another functionalizable atom on the heterocycle (or tether) is then deblocked and reacted with a further set of chemical substituents, which set may be the same or different from the original set, to give rise to an increasingly complex library of chemical compounds.

Appellant's specification teaches that, *inter alia*, a tether can be added in an iterative fashion (*i.e.*, to one functionalizable atom at a time). Thus, if one skilled in the art desired to prepare a mixture of at least six chemical compounds pursuant to claim 33 and desired the compounds to comprise only the tethers O and S, one skilled in the art would, based upon Appellant's specification, be guided to



provide for the O tether in one iteration and further provide for the S tether in another iteration, depending on the desired location of the tether with respect to the heterocyclic scaffold. The identity of the tethers as well as their location in the structures recited in claim 33 are up to the choice of the skilled artisan who practices the claimed invention.

In addition, Appellant's specification provides numerous examples whereby less than the entire alleged "genus" of "T" moieties is used. For example, page 27 of the specification depicts a reaction scheme whereby "T" is " $\text{N}(\text{CH}_2)_n\text{N}$ ,  $\text{N}(\text{CH}_2)_n\text{O}$ , and  $\text{NArN}$ ;" page 34 of the specification depicts a reaction scheme whereby "T" is "S;" page 39 of the specification depicts a reaction scheme whereby "T" is "alkoxy and aryloxy;" page 41 of the specification depicts a reaction scheme whereby "T" is "malonate;" page 49 of the specification depicts a reaction scheme whereby "T" is "O;" and page 50 of the specification depicts a reaction scheme whereby "T" is "Se." In each of these examples, "T" is other than a single bond, and "T" is other than the entire "genus" of "T" moieties alleged to be recited in claim 33. The examples are consistent with the teachings throughout Appellant's specification that individual "T" moieties can be selected as desired by the practitioner. Further, if one skilled in the art desired a mixture of compounds with, for example, only malonate, O, Se and S as tethers, one skilled in the art could prepare them based on Appellant's specification. The contrary position, that one skilled in the art desiring to prepare a mixture of at least six chemical compounds, all of which have tethers, would not be guided by Appellant's specification to remove the possibility where "T" is a single bond, is not credible and is not supported by any logical reasoning set forth in the Final Rejection. Indeed, one skilled in the art would simply add the desired tether at the desired location at the desired time, as instructed by Appellant's specification.

Appellant submits that it is established law that a specification that describes the claims as filed necessarily describes those embodiments following limiting amendments. *In re Johnson*, 194 U.S.P.Q. 187 (C.C.P.A. 1977). Indeed, the following language from *Johnson* at 196 is instructive:

The notion that one who fully discloses, and teaches those skilled in the art how to make and use, a genus and numerous species therewithin, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and has thus failed to satisfy the requirements of §112, first paragraph, appears to result from a hypertechnical application of legalistic prose relating to that provision of the

statute. All that happened here is that appellants narrowed their claims to avoid having them read on a lost interference count.

Likewise in the present application, all that happened here was that Appellant narrowed the claims to avoid the prior art. Accordingly, the amendment found in claim 33 does not constitute new matter, as asserted in the Final Rejection, because the scope of the amended claim is no broader than (and, thus, is supported by) the specification as filed. In view of this fact, reversal of the rejection for alleged lack of support is respectfully requested.

**B. Rejection Under 35 U.S.C. § 102(a)**

Claims 2-5, 7-12 and 33 have also been rejected under 35 U.S.C. § 102(a) for allegedly being anticipated by the Gordeev reference. The Final Rejection asserts at page 5 that some of the moieties in the library of compounds reported in the Gordeev reference (*i.e.*, the R<sub>3</sub> and R<sub>4</sub> moieties depicted on page 81 of the Gordeev reference), that are alleged to correspond to the “L” moieties recited in claim 33, are “attached to the ring via bonds.” Thus, the Final Rejection acknowledges that the compounds reported in the Gordeev reference have structures wherein at least one corresponding “T” moiety is a single bond. Appellant’s claim 33, as amended, recites that the “T” moieties are other than a single bond. The Final Rejection concludes:

Since the examiner deems applicant’s removal of the selection of T being a single bond from the Markush group in the instant claims to be new matter (see above), the rejection of the claims as being anticipated by Gordeev et al is maintained.

Thus, reversal of the new matter rejection presented above, in effect, reverses the rejection under 35 U.S.C. § 102(a) as well. Because the deletion of the phrase “is a single bond or” does not constitute new matter, the claimed invention is not anticipated by the Gordeev reference. Indeed, the Gordeev reference fails to teach compounds wherein all “T” moieties are other than a single bond, as recited in claim 33. Accordingly, reversal of the rejection under 35 U.S.C. § 102(a) is respectfully requested.

**DOCKET NO.: ISIS-2202**

**PATENT**

**IX. Conclusion**

The rejections of the pending claims under 35 U.S.C. § 112, first paragraph, and 35 U.S.C. 102(a) are improper and should be reversed. For the reasons given above, appealed claims 2-5, 7-12 and 33 are patentable.

Respectfully submitted,



Paul K. Legaard  
Registration No. 38,534

Date: **November 19, 2001**

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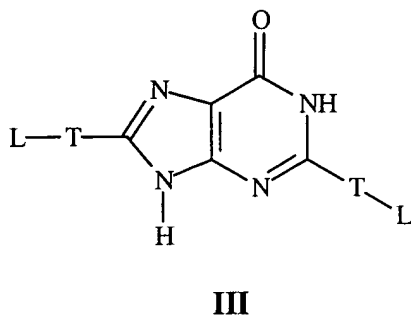
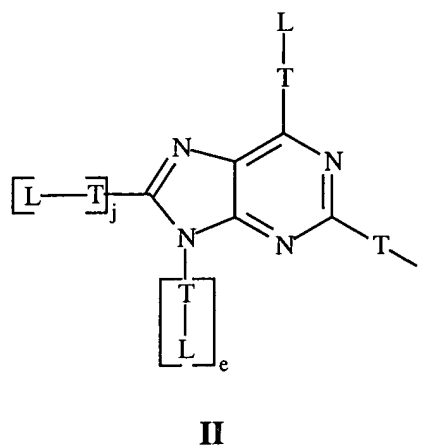
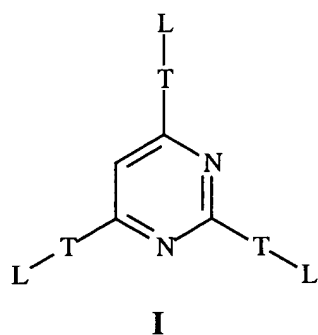
Examiner: M. Garcia

For: NUCLEOBASE HETEROCYCLIC COMBINATORIALIZATION

Assistant Commissioner of Patents  
Washington, D.C. 20231

APPENDIX "A" TO APPELLANT'S BRIEF

33. A mixture comprising a set of at least six chemical compounds having a common heterocyclic scaffold bearing functionalizable atoms, wherein said set of compounds is represented by one of structures I, II or III:



wherein for structure I:

each tether moiety T is -NH(R<sup>1</sup>)NH-, -NH(R<sup>1</sup>)O-, -NHR<sup>2</sup>NH-, -NHR<sup>2</sup>SO<sub>2</sub>NH-, -NHR<sup>1</sup>-, -N(R<sup>4</sup>)<sub>2</sub>, -N=N-, O, S, Se, -P(=O)(O)<sub>2</sub>, NH, OR<sup>2</sup>, OR<sup>3</sup>, malonato, pyrrolidinyl, piperidinyl, piperidinylmethylene, piperazinyl, or morpholino;

R<sup>1</sup> is alkylene; R<sup>2</sup> is aryl; R<sup>3</sup> is H or C<sub>1</sub>-C<sub>10</sub> alkyl; R<sup>4</sup> is alkyleneoxy; and

each chemical substituent L is, independently, C<sub>1</sub>-C<sub>10</sub> alkyl, substituted C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, substituted C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>2</sub>-C<sub>10</sub> alkynyl, substituted C<sub>2</sub>-C<sub>10</sub> alkynyl, C<sub>4</sub>-C<sub>7</sub> carbocyclic alkyl, substituted C<sub>4</sub>-C<sub>7</sub> carbocyclic alkyl, C<sub>4</sub>-C<sub>10</sub> alkenyl carbocyclic, substituted C<sub>4</sub>-C<sub>10</sub> alkenyl carbocyclic, C<sub>4</sub>-C<sub>10</sub> alkynyl carbocyclic, substituted C<sub>4</sub>-C<sub>10</sub> alkynyl carbocyclic, a nitrogen, oxygen or sulfur containing saturated heterocycle, a substituted nitrogen, oxygen or sulfur containing saturated heterocycle, a benzo-fused heterocycle, a substituted benzo-fused heterocycle, a substituted or unsubstituted saturated mixed heterocycle; wherein each of the substituent groups is selected from a group consisting of alkyl, alkenyl, alkynyl, aryl, hydroxyl, alkoxy, benzyl, nitro, thiol, thioalkyl, thioalkoxy and halo; or L is, independently, piperazine, pyridazine, pyrazine, triazine, phthalimido, an ether having 2 to 10 carbon atoms and 1 to 4 oxygen or sulfur atoms, hydrogen, halogen, hydroxyl, thiol, keto, carboxyl, NR<sup>1</sup>R<sup>2</sup>, CONR<sup>1</sup>, amidine, guanidine, glutamyl, nitro, nitrate, nitrile, trifluoromethyl, trifluoromethoxy, NH-alkyl, N-dialkyl, O-aralkyl, S-aralkyl, NH-aralkyl, azido, hydrazino, hydroxylamino, sulfoxide, sulfone, sulfide, disulfide, silyl, a nucleosidic base, an amino acid side chain, or a carbohydrate;

and for structures II and III:

each tether moiety T is -NH(R<sup>1</sup>)NH-, -NH(R<sup>1</sup>)O-, -NHR<sup>2</sup>NH-, -NHR<sup>2</sup>SO<sub>2</sub>NH-, -NHR<sup>1</sup>-, -N(R<sup>4</sup>)<sub>2</sub>, -N=N-, O, S, Se, -P(=O)(O)<sub>2</sub>, NH, OR<sup>2</sup>, OR<sup>3</sup>, malonato, pyrrolidinyl, piperidinyl, piperazinyl, morpholino, imidazolyl, pyrrolyl, pyrazolyl, indolyl, 1H-indolyl,  $\alpha$ -carbolinyl, carbazolyl, phenothiazinyl, phenoxazinyl, tetrazolyl, or triazolyl;

R<sup>1</sup> is alkylene; R<sup>2</sup> is aryl; R<sup>3</sup> is H or C<sub>1</sub>-C<sub>10</sub> alkyl; R<sup>4</sup> is alkyleneoxy; and

each chemical substituent L is, independently, C<sub>1</sub>-C<sub>10</sub> alkyl, substituted C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, substituted C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>2</sub>-C<sub>10</sub> alkynyl, substituted C<sub>2</sub>-C<sub>10</sub> alkynyl, C<sub>4</sub>-C<sub>7</sub> carbocyclic alkyl, substituted C<sub>4</sub>-C<sub>7</sub> carbocyclic alkyl, C<sub>4</sub>-C<sub>10</sub> alkenyl carbocyclic, substituted C<sub>4</sub>-C<sub>10</sub> alkenyl

carbocyclic, C<sub>4</sub>-C<sub>10</sub> alkynyl carbocyclic, substituted C<sub>4</sub>-C<sub>10</sub> alkynyl carbocyclic, C<sub>6</sub>-C<sub>14</sub> aryl, substituted C<sub>6</sub>-C<sub>14</sub> aryl, heteroaryl, substituted heteroaryl, a nitrogen, oxygen or sulfur containing heterocycle, a substituted nitrogen, oxygen or sulfur containing heterocycle, a mixed heterocycle, or a substituted mixed heterocycle; wherein each of the substituent groups is selected from a group consisting of alkyl, alkenyl, alkynyl, aryl, hydroxyl, alkoxy, benzyl, nitro, thiol, thioalkyl, thioalkoxy and halo; or L is, independently, phthalimido, an ether having 2 to 10 carbon atoms and 1 to 4 oxygen or sulfur atoms, hydrogen, halogen, hydroxyl, thiol, keto, carboxyl, NR<sup>1</sup>R<sup>2</sup>, CONR<sup>1</sup>, amidine, guanidine, glutamyl, nitro, nitrate, nitrile, trifluoromethyl, trifluoromethoxy, NH-alkyl, N-dialkyl, O-aralkyl, S-aralkyl, NH-aralkyl, azido, hydrazino, hydroxylamino, sulfoxide, sulfone, sulfide, disulfide, silyl, a nucleosidic base, an amino acid side chain, or a carbohydrate; and

each j and e is 0 or 1, with the sum of J and e equal to 1.

2. The mixture of claim 33 comprising at least ten chemical compounds.
3. The mixture of claim 33 comprising at least fifteen chemical compounds.
4. The mixture of claim 33 wherein said chemical compounds are within 20 mole percent of equimolarity in said mixture.
5. The mixture of claim 33 wherein said heterocyclic scaffold bears at least three functionalizable atoms.
7. The mixture of claim 33 wherein at least one of the functionalizable atoms on said heterocyclic scaffold is nitrogen, oxygen, or sulfur.
8. The mixture of claim 33 wherein said tether moiety bears at least one functionalizable atom.

9. The mixture of claim 8 wherein at least one functionalizable atom on said tether moiety is nitrogen, oxygen, or sulfur.
10. The mixture of claim 8 wherein the at least one functionalizable atom on the tether moiety is substituted with chemical substituents L.
11. The mixture of claim 10 wherein said chemical substituents comprise a leaving group prior to substitution on said tether moiety.
12. The mixture of claim 33 wherein said chemical substituents comprise a leaving group prior to substitution on said heterocyclic scaffold.